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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.
08/591,246	01/18/96	THOMSON J	960296.95723

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EXAMINER	
BRUMBACK, B	
ART UNIT	PAPER NUMBER
1815	#4

DATE MAILED: 03/27/97

Please find below and/or attached an Office communication concerning this application or proceeding.

Commissioner of Patents and Trademarks

Office Action Summary

Application No.	Applicant(s)
08/591,246	Thomson
Examiner	**Group Art Unit**
Brenda Brumback	1815

☐ Responsive to communication(s) filed on _____.

☐ This action is **FINAL**.

☐ Since this application is in condition for allowance except for formal matters, **prosecution as to the merits is closed** in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11; 453 O.G. 213.

A shortened statutory period for response to this action is set to expire 3 month(s), or thirty days, whichever is longer, from the mailing date of this communication. Failure to respond within the period for response will cause the application to become abandoned. (35 U.S.C. § 133). Extensions of time may be obtained under the provisions of 37 CFR 1.136(a).

Disposition of Claims

☒ Claim(s) 1-11 is/are pending in the application.

Of the above, claim(s) _____ is/are withdrawn from consideration.

☐ Claim(s) _____ is/are allowed.

☒ Claim(s) 1-11 is/are rejected.

☐ Claim(s) _____ is/are objected to.

☐ Claims _____ are subject to restriction or election requirement.

Application Papers

☒ See the attached Notice of Draftsperson's Patent Drawing Review, PTO-948.

☐ The drawing(s) filed on _____ is/are objected to by the Examiner.

☐ The proposed drawing correction, filed on _____ is ☐ approved ☐ disapproved.

☐ The specification is objected to by the Examiner.

☐ The oath or declaration is objected to by the Examiner.

Priority under 35 U.S.C. § 119

☐ Acknowledgement is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d).

☐ All ☐ Some* ☐ None of the CERTIFIED copies of the priority documents have been

☐ received.

☐ received in Application No. (Series Code/Serial Number) _____.

☐ received in this national stage application from the International Bureau (PCT Rule 17.2(a)).

*Certified copies not received: _____.

☐ Acknowledgement is made of a claim for domestic priority under 35 U.S.C. § 119(e).

Attachment(s)

☒ Notice of References Cited, PTO-892

☐ Information Disclosure Statement(s), PTO-1449, Paper No(s). _____

☐ Interview Summary, PTO-413

☒ Notice of Draftsperson's Patent Drawing Review, PTO-948

☐ Notice of Informal Patent Application, PTO-152

--- SEE OFFICE ACTION ON THE FOLLOWING PAGES ---

DETAILED ACTION

Claim Rejections - 35 USC § 112

1. Claims 1-11 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

a. Claim 1 is vague and indefinite, as it is drawn to a preparation of cells "which is capable of proliferation *in vitro* culture...". The syntax of the statement is incorrect. It is suggested that applicant amend this phrase to read "which is capable of proliferation in an *in vitro* culture...".

b. Claims 1 and 3 are vague and indefinite, as they are drawn to cell preparations of "normal karyotype". Applicant has failed to define the metes and bounds of "normal karyotype". Appropriate correction is required.

c. The meaning of the phrase "differentiate to derivatives..." in claim 1 is unclear. Rephrasing to "differentiate into derivatives..." would provide clarification.

d. Claim 9 is drawn to a method of isolating a cell line comprising (a) isolating a primate blastocyst and (b) isolating cells from ... the blastocyte. The term "blastocyte" lacks proper antecedent basis. It appears that the term "blastocyte" has been incorrectly substituted for "blastocyst". Appropriate clarification/correction is required.

2. The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

Claims 1-11 are rejected under 35 U.S.C. 112, first paragraph, as containing subject matter which was not set forth in the specification in such a way as to enable one skilled in the art to which it pertains, or with which it is most nearly connected, to make and/or use the invention.

a. The specification lacks complete deposit information for the deposit of the Rhesus monkey cell line designated on p. 26 of the instant specification as R 278.5, the cell line which appears to fulfill all of the conditions of the cell preparation of the instant invention. Although the instant specification (p. 32) also teaches five cell lines of marmoset derivation with normal karyotype and one cell line (designated Cj11) which has been maintained *in vitro* for greater than one year, it fails to teach both characteristics for the same cell preparation, as required in the claims of the instant invention. Therefore, the examiner has interpreted the specification to teach

that the Cj11 cell line does not fulfill all parameters of the cell preparation of the instant invention, thereby making R 278.5 the single working example of the instant invention.

b. While the specification provides enough information for one of skill in the art to produce a cell line with the same or similar properties as R278.5, reproduction of an identical cell line is an unpredictable event. Because it does not appear that R278.5 is known and publicly available or can be reproducibly isolated from nature without undue experimentation, a suitable deposit of R278.5 for patent purposes is required.

c. If a deposit was made under the provisions of the Budapest Treaty, filing of an affidavit or declaration by applicants or assignees, or a statement by an attorney of record over his or her signature and registration number, stating theat the deposit has been accepted by an International Depository Authority under the provisions of the Budapest Treaty, that all restrictions upon public access to the deposit will by irrevocable removed upon the grant of a patent on this application and that the deposit will bye replaced if viable samples cannot be dispensed by the depository, is required. This requirement is necessary when a deposit is made under the provision of the Budapest Treaty as the Treaty leaves these specific matters to the discretion of each State. Amendment of the specification to recite the date of the deposit and the complete name and address of the depository, and amendment of the claims to refer to the

accession number, is required. In addition, claims reciting the deposited material must be amended to include the depository accession number of the deposited material.

c. Furthermore, unless a deposit was made at or before the time of filing, a declaration filed under the 37 C.F.R. 1/132 is necessary to construct a chain of custody. The declaration, executed by a person in a position to know, should identify the deposited cell line by its depository accession number, establish that the deposited cell line is the same as that described in the specification, and establish that the deposited cell line was in applicant's possession at the time of filing. See In re Lundak, 773 F.2d. 1216, 227 U.S.P.?Q. 90 (Fed. Cir. 1985).

Double Patenting

3. A rejection based on double patenting of the "same invention" type finds its support in the language of 35 U.S.C. 101 which states that "whoever invents or discovers any new and useful process ... may obtain a patent therefor ..." (Emphasis added). Thus, the term "same invention," in this context, means an invention drawn to identical subject matter. *Miller v. Eagle Mfg. Co.*, 151 U.S. 186 (1894); *In re Ockert*, 245 F.2d 467, 114 USPQ 330 (CCPA 1957); and *In re Vogel*, 422 F.2d 438, 164 USPQ 619 (CCPA 1970).

A statutory type (35 U.S.C. 101) double patenting rejection can be overcome by canceling or amending the conflicting claims so they are no longer coextensive in scope. The filing of a terminal disclaimer cannot overcome a double patenting rejection based upon 35 U.S.C. 101.

Claims 1-11 are provisionally rejected under 35 U.S.C. 101 as claiming the same invention as that of claims 1-11 of copending Application No. 08/376,327. This is a provisional double patenting rejection since the conflicting claims have not in fact been patented.

Claim Rejections - 35 USC § 102/103

4. Claims 1-8 and 11 are rejected under 35 U.S.C. 102(a) as anticipated by or, in the alternative, under 35 U.S.C. 103(a), as obvious over Nation/World (Nov.4, 1994). Nation/World discloses isolated primate embryonic stem cells from Rhesus monkeys and marmosets and teaches that these cells are the parent cells of many body tissues. Nation/World further teaches that these cells can be induced to grow into any kind of tissue. While Nation/World does not disclose the specific morphological characteristics of the claims of the instant invention, these characteristics are inherent to the cells disclosed by Nation/World. The method of obtaining the cell preparation does not appear to patentable distinguish the embryonic stem cells from the prior art. Therefore, the claimed invention would have been at least *prima facie* obvious, if not anticipated by, one of

ordinary skill in the art at the time the invention was made, absent clear and convincing evidence to the contrary.

Claim Rejections - 35 USC § 103

5. The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

Claims 1, 7, and 8 are rejected under 35 U.S.C. 103(a) as being unpatentable over Bongso, et al. ("Isolation and culture of inner cell mass cells from human blastocysts", Human Reproduction, vol. 9:2110-2117 [1994]) in view of Dyer, et al. (WO 94/03585) and Hogan (U.S. Patent 5,453,357).

a. Bongso, et al. describe a purified preparation of human embryonic stem cells (SC) of normal karyotype grown on an epithelial cell feeder layer for two passages. Bongso, et al. describe the SC as alkaline phosphatase positive. Bongso, et al. do not describe long term culture of human ES cells on fibroblast feeder layers.

b. Dyer, et al. describe maintaining a culture of ES cells of varied species *in vitro* without differentiation in the presence of a feeder layer of chicken embryonic fibroblasts (see p.2, lines 9-12; p.2, lines 28-29; and p.3, line 1). Dyer, et al. further describe these cells as pluripotent in that they are capable of differentiating *in vivo* into various cell types of all three primary germ layers (see p.10, lines 28-29) when removed from the feeder layers. Dyer, et al. do not describe culture of ES cells for long periods.

c. Hogan teaches long term culture of non-mouse pluripotent ES cells for indefinite periods (indefinite to include the greater than one year range stipulated in claim 1; see column 4, lines 22-24) by maintaining the cells on feeder layers and administering growth enhancers. Hogan further teaches the retention of normal karyotype through long term culture (see column 8, lines 17-19) and differentiation of the cells when removed form the feeder layers to monolayer culture, giving rise to embroid bodies and multiple differentiated cell phenotypes (see the abstract).

d. It would have been *prima facie* obvious to one of ordinary skill in the art at the time the invention was made to have combined the teachings of Dyer, et al. that ES cells grow well in long term culture in an undifferentiated state on feeder layers of embryonic fibroblasts with the teachings of Hogan that cells can be maintained for long periods of time on feeder layers with growth enhancers while maintaining a normal karyotype and the ability to differentiate when removed form the feeder layers to improve the success of the methods taught by Bongso, et al.,

thus allowing maintenance of primate ES cells in culture for long periods. One of ordinary skill in the art at the time the invention was made would have been motivated to do so because Bongso, et al. teach that such a cell preparation would have beneficial uses in treatment of neurodegenerative and genetic disorders and as a model in studying the events involved in embryogenesis and genomic manipulation (see the abstract). Furthermore, in the absence of evidence to the contrary, it would be expected that factors supplied to the stem cells by the cells of the feeder layers would be at insufficient concentrations when ES cells are grown to high density and therefore, the ES cells would spontaneously differentiate.

6. Claims 2-6 are rejected under 35 U.S.C. 103(a) as being unpatentable over Bongso, et al., Dyer, et al., and Hogan as applied to claims 1,7, and 8 above, and further in view of Damajanov, et al.("Retinoic acid-induced differentiation of the developmentally pluripotent human germ cell tumor-derived cell line, NCCIT", Laboratory Investigation, 68:220-232 [1993]).

a. The combined teachings of Bongso, Dyer, and Hogan are to purified preparations of ES cells of normal karyotype (including human cells) which remain undifferentiated when cultured over time on feeder layers of embryonic fibroblasts or other cells and which spontaneously differentiate upon removal from the feeder layers. Bongso, Dyer, and Hogan do not teach ES cells negative for SSEA-1, but positive for SSEA-3, SSEA-4, TRA-1-60, and TRA-1-81 markers.

b. Damjanov, et al. teach that human ES cells do not express SSEA-1, but do express SSEA-3, SSEA-4, TRA-1-60, and TRA-1-81. Damjanov, et al. further teach these markers as differentiating human ES cells from mouse ES cells (see p.225, *Cell Surface Antigens*, paragraphs 1 and 2). Damjanov, et al. also teach that human ES cells secrete chorionic gonadotropin when differentiated (see p. 223, column 2, lines 1-5; and p. 224, Figure 6). One of ordinary skill in the art at the time the invention was made would have found it *prima facie* obvious to use the markers taught by Damjanov, et al. as specific for human cells to characterize the cell preparation of Bongso, since it would be expected that the human ES cells of Bongso would contain these markers, as taught by Damjanov, et al. One of ordinary skill in the art at the time the invention was made would have been motivated to do so to ensure that cells used for *in vivo* therapy, as taught by Bongso, et al., were of human derivation to prevent problems associated with inoculation of cells of a heterologous species.

7. Claims 9-11 are rejected under 35 U.S.C. 103(a) as being unpatentable over Bongso, et al. in view of Brown, et al.("Criteria that optimize the potential of murine embryonic stem cells for in vitro and in vivo developmental studies", In Vitro Cell. Dev. Biol. 28A:773-778, Nov.-Dec. 1992).

a. Bongso, et al. describe a method of isolating human ES cells comprising the steps of isolating a human blastocyst, isolating cells from the inner cell mass, plating the inner cell mass

cells on epithelial feeder monolayers for formation of inner cell mass lumps, dissociating the lumps, and replating the dissociated cells. Bongso, et al. do not teach replating the cells on fibroblast feeder layers.

b. Brown, et al. teach that cell growth of the disaggregated embryonic cells from the inner cell masses or lumps is improved when the cells are replated onto embryonic fibroblast feeder layers over plating the disaggregated cells onto gelatin substrates (see p. 775, column 2, paragraph 2) and further that retaining the feeder layer helps to obtain ES cell lines at an increased level of efficiency (see paragraph 3, lines 4-6). Brown, et al. do not teach culture of primate ES cells using feeder layers.

c. It would have been *prima facie* obvious to one of ordinary skill in the art at the time the invention was made to have applied the teachings of Brown, et al. to the method taught by Bongso, et al. to increase the number of passages of human ES cells and optimize the chances of obtaining a human ES cell line.

8. Any inquiry concerning this communication or earlier communications from the examiner should be directed to Brenda Brumback whose telephone number is (703) 306-3220. If the examiner can not be reached, inquiries can be directed to Primary Examiner Michael Woodward whose telephone number is (703) 308-3890 or Supervisory Patent Examiner Marian Knode

whose telephone number is (703) 308-4311. Any inquiry of a general nature or relating to the status of this application should be directed to the Group receptionist whose telephone number is (703) 308-0196.

Papers related to this application may be submitted to Group 1800 by facsimile transmission. Papers should be faxed to Examiner Brenda Brumback, Art Unit 1815 and should be marked "OFFICIAL" for entry into prosecution history or "DRAFT" for consideration by the examiner without entry. The Art Unit 1815 FAX telephone number is (703)-305-7939. FAX machines will be available to receive transmissions 24 hours a day. In compliance with 1096 OG 30, the filing date accorded to each OFFICIAL fax transmission will be determined by the FAX machine's stamped date found on the last page of the transmission, unless that date is a Saturday, Sunday or Federal Holiday with the District of Columbia, in which case the OFFICIAL date of receipt will be the next business day.

Brenda Brumback

March 20, 1997

MICHAEL P. WOODWARD
PRIMARY EXAMINER
GROUP 1800